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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KOLKER, DANIEL E	
ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 10/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/194,619	KENNETH, HOWARD	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *9-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-27* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's remarks filed 22 August 2005 have been entered. Claims 1 – 27 are pending.

Election/Restrictions

2. Applicant's election with traverse of Group I in the reply filed on 22 August 2005 is acknowledged. The traversal is on the ground(s) that claim 1 does in fact constitute a contribution over the prior art and thus the examiner's finding of lack of unity of invention is incorrect. This is not found persuasive for the following reasons:

Applicant argues, on p. 1 of the remarks, that the claims relate to the detection of stress protein expression and that May (1985) does not report stress protein expression. Applicant's arguments have been fully considered but are not persuasive. The examiner indicated on p. 3 of the restriction requirement that the first technical feature is a cell culture of fibroblast cells from a patient having a pre-determined neurological disease. Since May fairly teaches cultures of fibroblasts from patients known to have Huntington's disease the first technical feature is not a contribution over the prior art and therefore the claims lack unity.

Furthermore, claim 1, part (d) does not recite detection of stress protein expression, but rather recites use of an indicator system which is capable of detecting same. The tryptan blue assay measures whether or not cells are dead or alive, and since excessive stress protein expression is correlated with cell death the assay used by May is an indicator system capable of detecting stress protein expression. The correlation between stress protein expression and cell death was well-known in the prior art. For example, Kawagoe (1993. Journal of Neurochemistry 61:254-260) teaches that transient global ischemia leads to both induction of HSP70 and cell death. Applicant argues that induction of stress protein expression is a compensatory mechanism that can attenuate cell death, but this point is not germane to the question of whether measuring cell death constitutes use of an indicator system capable of detecting stress protein expression. Since both cell death and induction of stress proteins are consequences of cellular insult, such as that induced by ischemia or reactive oxygen species, measuring cell death clearly is capable of detecting stress protein expression.

The requirement is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

3. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Objections

4. Claim 1 is objected to because of the following informalities: The word "concomitant" on the first line of step (c) is misspelled. Appropriate correction is required.

Claim Rejections - 35 USC §§ 101 and 112

5. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1 – 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of contacting cultured fibroblasts with agents under investigation wherein the pathological mechanism is manifest in both neural cells and fibroblasts, does not reasonably provide enablement for a method of screening for drugs which are candidates for treatment of all neurological diseases, or for determining whether or not the agent in the screening assay should be selected as a drug candidate agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6)

breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

The nature of the invention, a method of screening for candidate compounds for treatment of neurological disease by assaying fibroblasts, is complex. Fibroblasts differ from neurons in many ways, including their morphology, excitability, and their developmental lineage (fibroblasts are derived from mesoderm whereas neurons are derived from ectoderm). Thus a skilled artisan would not expect that fibroblasts are generally representative of neural disease. On p. 21, first complete paragraph, of the specification applicant lists many neurological diseases and asserts that the claimed method could be used to find candidates for treatment of these diseases. These disease are all inherited diseases and thus the underlying mechanism, a mutation in the DNA, would be expected to be found in all cells of the body. However the claims as written include all neurological diseases. Many diseases, for example schizophrenia, febrile seizures, Korsakoff's syndrome, spongiform encephalopathies, and many forms of Alzheimer's disease are all caused by non-genetic factors. Korsakoff's syndrome is a neurological disease characterized by memory loss and is caused by excessive alcohol consumption and a lack of B vitamins (see Kandel et al. Principles of Neural Science 1994. p. 1006). Spongiform encephalopathies can be acquired by eating tainted food. Febrile seizures are caused by excessive fever, many other forms of epilepsy have other, non-genetic causes (see Merck Manual Second Home Edition, Chapter 85). The mechanisms underlying these neurological diseases would not be expected to be reflected in fibroblasts, given the different physiological characteristics of fibroblasts and neurons, combined with the non-genetic nature of these diseases.

The working examples in the specification are all drawn to assaying for drugs which could treat Charcot-Marie-Tooth disease, which is a genetic disease. Thus the only disease for which the claims are clearly enabled is Charcot-Marie-Tooth disease. The claims are broad in that they are drawn to assays to find drugs for treatment of any disease. However given the state of the prior art, the lack of guidance on how to use the method to identify drugs for treatment of non-genetic diseases, and the complex nature of the invention, a skilled artisan would have to resort to undue experimentation in order to practice these methods commensurate in scope with the claims.

While the specification discloses the results of an experiment in which fibroblasts from patients with Charcot-Marie-Tooth disease show a different staining pattern on a two-dimensional gel compared to fibroblasts from unaffected controls, and teaches the artisan how a screening assay could be performed, the specification does not in fact provide working examples of the screening assay. There is no disclosure of experiments in which the method as claimed was performed. Furthermore, as claim 1 is presently written it requires the use of an indicator system, but the claim does not guide the artisan sufficiently in how to use that indicator system, nor does it guide the artisan in deciding which agents under investigation should be selected as drug candidate agents.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1 – 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, part (d) provides for the use of an indicator system, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced. Because claims 2 – 8 depend from claim 1 they also stand rejected

9. Claims 1 – 8 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

10. Claims 1 – 8 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: determining whether or not the agent is a candidate of possible clinical value. Because claim 1, part (d) is indefinite for the reasons enumerated above, the method recited is incomplete. Merely growing the six cultures concomitantly will not provide the skilled artisan with guidance as to whether or not the agent being investigated qualifies as a drug candidate agent. Since steps (a) – (c) of claim 1 do not by themselves

constitute a screening method, the steps fail to accomplish the goal in the preamble and thus the claim is not complete.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by May (1985. Journal of the Neurological Science 70:101-112, cited in previous office action), as evidenced by Kawagoe (1993. Journal of Neurochemistry 61:254-260).

May teaches concomitant culture of fibroblasts from patients with Huntington's disease and from control patients. The specific cell lines and culture conditions are detailed in the first paragraph of p. 103. May et al. teach growth of these cultures in the absence of any candidate agents, which correspond to claim 1, parts (a) and (b) and claim 1(c)(1) and 1(c)(2). They also teach culture of the cells in the presence of a drug candidate agent, namely the antioxidant propyl gallate (see p. 108, first complete paragraph). This corresponds to claim 1(c)(3) and 1(c)(4). Furthermore they tested the control culture in the presence of a chemical stress protein-inducing parameter with and without the agent. The chemical stress protein-inducing parameter was 15mM L-HCA (see p. 108, first complete paragraph). This corresponds to claim 1(c)(5) and 1(c)(6). Finally, May et al. used an indicator system capable of detecting stress protein expression. The indicator system was the percentage of cells which are viable; since cells die upon sufficient levels of stress protein the viability assay corresponds to claim 1(d) as viability tests fairly anticipate use of an indicator system. Kawagoe provides evidence that transient global ischemia leads to both induction of HSP70 and cell death and thus by measuring viability May fairly used an indicator system that is capable of detecting stress protein expression.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 1, 2, and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over May (1985. Journal of the Neurological Science 70:101-112, cited in previous office action), Berberian (WO 91/15219, published 17 October 1991), and Ide (1995. Biochemical and Biophysical Research Communication 209:1119-1125).

May teaches a screening assay that uses the six groups of fibroblasts recited in claim 1, as set forth in the rejection under 35 USC 102(b). May does not teach antibodies specific for stress proteins indicative of oxidative stress or resolution of stress proteins according to molecular weight.

Berberian teaches methods of detecting heat shock protein 70 (HSP 70), using primary antibodies specific for the stress protein (antibody N27F34, which Berberian teaches is specific for two forms of HSP 70) followed by anti immunoglobulin HRP-conjugated secondary antibody and also using gel electrophoresis. See p. 16, lines 14 – 27. Berberian also teaches that HSP 70 is induced by the presence of abnormal proteins (see p. 2 lines 15 – 31). Berberian does not teach detecting HSP 70 in fibroblasts from patients with Huntington's disease.

Ide teaches that Huntington's disease leads to the presence of abnormal proteins within the cell. Specifically, the 350kDa protein, named p350 in Ide (and now known as Huntingtin) shows an increased molecular mass in tissue from patients with Huntington's disease.

It would have been obvious to one of ordinary skill in the art to screen drugs using the method of May, and to use either a combination of primary and secondary antibodies or gel electrophoresis, as taught by Berberian, with a reasonable expectation of success. The motivation for using the antibody method would be to detect HSP 70, as Berberian teaches HSP 70 is induced by abnormal proteins and Ide teaches that Huntington's disease is characterized by abnormal proteins. It would also be obvious to use a gel resolution technique, as taught by Berberian, with a reasonable expectation of success. The motivation to do so would be to separate the two HSPs which are recognized by N27F34. Berberian teaches that the 73kD species is constitutive whereas the 72kD species is inducible, and since he also teaches that it is the inducible forms of HSPs which show increased expression in the presence of cellular abnormalities (see p. 2), the artisan would be immediately motivated to separate these two species of HSP on a gel.

15. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over May, Berberian, and Ide as applied to claims 1 and 2 above, and further in view of Savage et al. (1992. Avidin-Biotin Chemistry: A Handbook. Rockford, Illinois: Pierce Chemical Company, pp. 191 – 194). None of May, Berberian, or Ide teach antibody-indicator conjugates include biotin.

Savage teaches detection in immunohistochemical techniques using biotin. It would have been obvious to one ordinary skill in the art to use a biotin-labeled antibody in the screening method, with a reasonable expectation of success. The motivation to do so would be to improve detection, and Savage in fact provides this motivation on p. 191.

16. Claims 1 and 5 – 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over May (1985. Journal of the Neurological Science 70:101-112, cited in previous office action), Bowling (1995. Life Sciences 56(14):1151-1171) and Levine (1994. Methods in Enzymology 233:346-357).

May teaches a screening assay that uses the six groups of fibroblasts recited in claim 1, as set forth in the rejection under 35 USC 102(b). May does not teach detecting a protein containing a structural modification indicative of oxidative stress.

Bowling teaches that Huntington's disease is characterized by many forms of altered metabolism, including increased lactate levels and lipofuscin accumulation and teaches that lipofuscin levels in particular are indicative of oxidative stress (see pp. 1159 – 1160). Furthermore Bowling teaches that impaired metabolism leads to oxidative stress (see pp. 1152 – 1153 and Figure 1). Bowling does not teach how to detect a protein containing a structural modification indicative of oxidative stress.

Levine teaches that carbonyl groups are added to proteins when they are exposed to free radicals, and teaches methods of detecting the carbonyl groups with 2,4-dinitrophenylhydrazine. These methods include gel electrophoresis to separate the proteins and detection with primary antibody against 2,4 dinitrophenyl moieties and biotin-labeled second antibodies (see p. 355).

It would have been obvious to one of ordinary skill in the art to use the detection system of Levine in the assay taught by May, with a reasonable expectation of success. The motivation to do so would be to screen for drugs which are candidates for treatment of Huntington's disease. Since Bowling teaches that Huntington's disease is characterized by increased levels of oxidative stress, the artisan of ordinary skill would be motivated to use an assay that detects free-radical-induced damage such as that taught by Levine. Furthermore the teachings of May

are also drawn to the effects of free radicals on cells, and thus it would be reasonable to expect success when combining these teachings, as they are all drawn to the effects of free radicals on biological systems.

Conclusion

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel E. Kolker, Ph.D.
October 12, 2005

SHARON TURNER, PH.D.
PRIMARY EXAMINER
10-12-05